**UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF NEW JERSEY**
**CAMDEN VICINAGE**

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| **IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION**<br><br>**This Document Relates to All Actions** | MDL No. 2875<br><br>Honorable Robert B. Kugler, District Court Judge<br><br>Oral Argument Requested |

# DEFENDANTS' REPLY IN SUPPORT OF THEIR JOINT MOTION TO EXCLUDE THE OPINIONS OF DIPAK PANIGRAHY, M.D.

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## Rules

Plaintiffs' Brief in Opposition to Defendants' Motion to Exclude the Opinions of Dipak Panigrahy, M.D. (the "Opposition" or "Opp.") fails to adequately address Defendants' challenges to the reliability of Dr. Panigrahy's methodology, the fit of his opinions to the case, and Dr. Panigrahy's qualifications. Plaintiffs do not point to any qualifications Dr. Panigrahy possesses with respect to genotoxic compounds and cancer development—the specific opinions Dr. Panigrahy is offering in the case—and instead focus generally on Dr. Panigrahy's background with cancer research. Plaintiffs likewise do not reconcile the analytical gaps underlying Dr. Panigrahy's methodology. Dr. Panigrahy frames the general causation inquiry by focusing on the carcinogenicity of NDMA and NDEA generally without considering the levels of NDMA and NDEA in VCDs, *i.e.*, the dose, or whether those levels (or any level) of NDMA or NDEA are capable of causing the specific cancers identified by Plaintiffs as being at issue in this litigation, *i.e.*, the response. Dr. Panigrahy's improper framing of the general causation inquiry taints his analysis and results in opinions which will not help the Court or the trier of fact determine the question of general causation.

Plaintiffs similarly attempt to address the numerous flaws in Dr. Panigrahy's methodology by reframing the general causation inquiry in a further unhelpful manner while still failing to account for dose or response. But dose, that is the level of exposure a plaintiff taking VCDs could reasonably have been exposed to, and the

response it provokes, cannot be separated from the causation inquiry, even at the general causation stage. Plaintiffs' reliance on a lifetime cumulative exposure theory in their class certification briefing (*see* Dkt. 1750 at 4) shows that Plaintiffs understand that dose/response is a critical component of the causation analysis. Likewise, the main case upon which Plaintiffs rely in their Opposition, *In re Roundup Products Liability Litigation*, 390 F. Supp. 3d 1102, 1108 (N.D. Cal. 2018), also makes it clear that dose/response cannot be separated from the causation inquiry. Accordingly, Defendants respectfully request that the Court exclude Dr. Panigrahy's opinions.

## ARGUMENT

### I. PLAINTIFFS FAIL TO ADDRESS DR. PANIGRAHY'S FLAWED METHODOLOGY OR THE FLAWED DATA UPON WHICH HE RELIES.

#### A. Plaintiffs' Reliance on *Roundup* Is Misplaced.

Plaintiffs respond to Defendants' challenge to Dr. Panigrahy's methodology by asserting that Dr. Panigrahy used "the totality of scientific evidence to support a carcinogenicity determination." *See* Opp. at 6. The problem with Dr. Panigrahy's methodology, however, is not the breadth of the sources on which he relied but rather the analytical leaps he made in assessing the various studies he reviewed. These analytical leaps are largely the result of Dr. Panigrahy attempting to answer whether the NDMA or NDEA in VCDs causes cancer in humans without giving consideration to dose, response, first-pass metabolism, and DNA repair. Plaintiffs

rely heavily on *Roundup* and attempt to align Dr. Panigrahy with the *Roundup* experts who were permitted to testify. Plaintiffs note that Dr. Panigrahy and "Plaintiffs' experts in *Roundup* used the Bradford Hill criteria and surveyed a significant amount of epidemiological evidence, including occupational studies, as well as animal studies, and mechanistic data." *See* Opposition at 8. Plaintiffs thus assert that simply showing that Dr. Panigrahy reviewed certain categories of studies and data renders his methodology sound. Plaintiffs, however, present a drastic oversimplification of the *Roundup* decision and the factors that render an expert's methodology sound for purposes of a Rule 702 and *Daubert* analysis.

As the *Roundup* court noted, the experts' testimony was ultimately admitted there (despite the court noting it was a close call) because the literature the experts reviewed was relevant to the question of whether glyphosate can cause a single type of cancer—Non-Hodgkin's Lymphoma *at human-relevant doses*. *See Roundup*, 390 F. Supp. 3d at 1151 ("They have surveyed the significant body of epidemiological literature *relevant to this question*.") (emphasis added). "Because [the experts] . . . went beyond the inquiry conducted by IARC, offering independent and relatively comprehensive opinions that the epidemiological and other evidence demonstrates glyphosate causes NHL in some people who are exposed to it" the opinions are admissible. *Id.* at 1109. The *Roundup* court discussed in great detail the importance of the expert's testimony and analysis being tailored to the specific inquiry, noting

that simply relying on (or following) a public health's agency's determination that a compound is "probably carcinogenic to humans" does not satisfy the relevant inquiry for civil litigation. *Id.* at 1108. "[The] decision that a substance is 'probably carcinogenic to humans' is a hazard assessment—merely the first step in determining whether the substance currently presents a meaningful risk to human health." *Id.* "At this general causation phase, the question is whether a reasonable jury could conclude by a preponderance of the evidence that glyphosate can cause NHL *at exposure levels people realistically could have experienced*." *Id.* (emphasis added). Accordingly, the determining factor in *Roundup* was not simply what the experts considered but also its relevance to the particular general causation inquiry in that case. And as noted, the *Roundup* court was considering general causation for a single cancer (Non-Hodgkin's Lymphoma) and required evidence connecting that cancer to the plaintiffs' reasonable exposure to the chemical at issue. Applying *Roundup* here, as Plaintiffs urge, requires the same dose-specific and cancer-specific showing for each cancer alleged by Plaintiffs, based on exposure to NDMA or NDEA at the doses to which Plaintiffs could have been reasonably exposed.

With respect to the specific methodology the experts employed in *Roundup*, the court assessed *each* expert's particular analysis to ensure reliability. Whether their testimony was ultimately admitted was not based simply on "the type of available scientific evidence" the expert reviewed, *see* Opp. at 9, but rather whether

"the analytical leaps required to reach [the experts'] ultimate conclusions regarding glysophate's ability to cause NHL in humans are supportable, in light of the evidence on which they relied." 390 F. Supp. 3d at 1131. Here, as noted in Defendants' initial brief, Dr. Panigrahy's conclusions are not supported by the evidence that he considered. The flaws in his analysis are beyond those deemed acceptable in *Roundup*.[1] Dr. Panigrahy did not consider studies showing "biological effects at relatively low doses." *Id.* at 1144. Among other things, he relies on studies where NDMA exposure was significantly higher than the exposure levels at issue here; he relies on a single molecule theory (despite Plaintiffs' contention that he did not); he ignores the role of DNA repair, despite simultaneously acknowledging that DNA repair can result in error-free repair of mutation-causing adducts; and while he did not consider the issue of first-pass metabolism or the level that can be completely metabolized by the liver, he opines without support that the NDMA in VCDs would escape first-pass metabolism in the liver. Notably, Dr. Panigrahy admitted there is some level of NDMA that would *not* escape the liver and therefore not reach any

[1] Similarly, Plaintiffs' reliance on *In re Actos Prods. Liab. Litig.*, MDL 2299, 2013 WL 6796461 (W.D. La Dec. 19, 2013) is also misplaced as the facts of that case and the studies the experts relied on are distinguishable. The issue in *Actos* largely related to whether cancer could develop within one year of exposure to the drug at issue. There were also human clinical studies upon which the plaintiffs' experts relied. Moreover, the plaintiffs' experts were analyzed collectively in that case, in light of the plaintiffs' particular general causation theory.

downstream organs, *see* Panigrahy Dep., Dkt. 1716-4, at 441:17-23, but he does not know what that level is. The analytical leaps Dr. Panigrahy takes are too broad to be logically grounded in the evidence and studies he reviewed. Dr. Panigrahy's methodology is flawed and unreliable, and his opinions should be excluded.

### B. There Is No Question that Dr. Panigrahy Relies on a "Single Molecule Theory."

Plaintiffs assert that Defendants "repeatedly misrepresent[], misstate[] and misconstrue[] Dr. Panigrahy's testimony, report, methodology and opinions" by pointing out that Dr. Panigrahy relies on a single molecule theory, which Plaintiffs attempt to deny. *See* Opp. at 9. Plaintiffs' surprising assertion that Dr. Panigrahy does not use a single molecule theory in reaching his opinions is incredible and directly contradicts Dr. Panigrahy's report and his deposition testimony where he repeatedly acknowledged this opinion.

> Q: You've expressed an opinion multiple times that you think one molecule would be a sufficient—that one molecule can cause cancer. You've said that, correct?
>
> A: Yes.
>
> . . .
>
> A: The question here is the NDMA, in the valsartan tablet, is it causing cancer in humans. **And here—one molecule can cause cancer.**

Panigrahy Dep., Dkt. 1716-4, at 365:16-366:6 (emphasis added).

Defendants have neither misstated nor misrepresented Dr. Panigrahy's

testimony and opinions; they have quoted him. Plaintiffs, by contrast, ask the Court to disregard Dr. Panigrahy's sworn testimony in favor of their mischaracterizations of his opinions. Plaintiffs state that when Dr. Panigrahy references "one molecule," he is explaining the process of molecular DNA damage that can lead to mutations and initiate the process that causes cancer. *See* Opp. at 9-10. That is exactly the flaw Defendants pointed out in their initial brief. *See* Motion at 7 ("Dr. Panigrahy thus believes, incorrectly, that because exposure to one molecule of NDMA can allegedly induce DNA damage, exposure to one molecule is capable of causing cancer."). Plaintiffs' belated attempt to sidestep Dr. Panigrahy's single molecule theory by asserting that Dr. Panigrahy states that one molecule of NDMA "can" cause cancer but not that one molecule "will likely cause cancer," *see* Opp. at 10 n.23, is a distinction without a difference. This is particularly apparent through Dr. Panigrahy's opinion that there is no safe exposure threshold for NDMA and NDEA. *See id.* at 10. ("This is why there is no safe exposure threshold for genotoxic chemicals like NDMA and NDEA, and . . . one molecule of NDMA or NDEA can disrupt the DNA and lead to mutation that can lead to cancer."). It is contradictory for Dr. Panigrahy to assert, on the one hand, that he is *not* relying on a single molecule theory yet, on the other hand, continue to subscribe to his opinion that there

is no safe exposure threshold for NDMA and NDEA.[2] The two are obviously at odds, and Plaintiffs' Opposition cannot reconcile them.

The question of whether lifetime cumulative exposure has been accepted by other courts says nothing about whether Dr. Panigrahy assessed lifetime cumulative exposure reliably here. As noted in Defendants' initial brief, Dr. Panigrahy's cumulative exposure assessment was far from reliable.[3] The Hidajat study, for example, involved NDMA exposure levels exponentially higher than those associated with any VCDs, and Dr. Panigrahy could not identify any valsartan patient who could have been exposed to the levels of NDMA identified in Hidajat. Panigrahy Dep., Dkt. 1716-4, at 497:20-499:8.

In addition, Dr. Panigrahy used the highest level of NDMA and NDEA in assessing cumulative exposure, instead of assessing the levels to which valsartan patients could have reasonably been exposed. Plaintiffs attempt to clean this up by misstating the general causation question as whether "NDMA and NDEA can cause

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[2] Plaintiffs suggest in their opposition that Dr. Panigrahy "addresses the 'no safe level' and 'no observed effect level' concepts as they apply to genotoxins generally. But Dr. Panigrahy repeatedly testified in his deposition that his opinion that there was no safe level related not just to genotoxins generally but rather specifically to NDMA and NDEA. *See, e.g.*, Panigrahy Dep., Dkt. 1716-4, at 184:21-185:8; 203:2-25; 316:11-14; 357:3-8.

[3] Even if the Court were to deem Dr. Panigrahy's lifetime cumulative exposure analysis reliable, Dr. Panigrahy's reliance on a single molecule theory should nonetheless be excluded as unreliable and unhelpful to the finder of fact.

the various human cancers when people are exposed to the doses people might plausibly experience." *See* Opp. at 21. But the question even at the general causation stage is not an abstract hypothetical exposure level a person "might plausibly experience," but rather whether valsartan can cause the various specific human cancers at issue at the level to which a patient could plausibly have been exposed by the VCDs at issue. Put another way, the focus must be on the trace levels of NDMA/NDEA measured in the VCDs, not a theoretical level no valsartan patient could have ingested. Assessing the relevant doses to which Plaintiffs could have been reasonably exposed, and the response to such doses, is critical.[4] It is unreasonable and implausible to assume that any one plaintiff could have taken the valsartan from the highest single lot measured and received that same highest lot for each and every prescription refill. Dr. Panigrahy's failure to properly consider the plaintiffs' reasonable exposure reveals the disqualifying flaws in his methodology. His cumulative exposure assessment therefore should be excluded as unreliable

[4] Defendants hereby refer the Court to and incorporate by reference the case law cited in Section II. A. of Defendants' Reply in Support of Their Joint Motion to Exclude the Opinions of Steven Hecht, Ph.D, including but not limited to *In re Lipitor (Atorvastatin Calcium) Mktg. Sales Practices & Prods. Liab. Litig.*, 2015 WL 6941132, at *1 (D.S.C. Oct. 22, 2015); *In re Prempro Prods. Liab. Litig.*, 738 F. Supp. 2d 887, 895 (E.D. Ark. 2010); *In re Accutane Products Liab.*, 511 F. Supp. 2d 1288, 1293 (M.D. Fla. 2007); *In re Zoloft (Sertraline Hydrocloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 466, 477 (E.D. Pa. 2014); *Daniels-Feasel v. Forest Pharm., Inc.*, 2021 WL 4037820, at *15 (S.D.N.Y. Sept. 3, 2021).

because it is not scientifically sound.

### C. Defendants Do Not Conflate General and Specific Causation.

Plaintiffs assert Defendants have applied the wrong standard at the general casuation stage, stating that "general causation is whether a substance can cause an increased risk of a particular injury or condition in the general population." *See* Opp. at 20 (citing *McClain v. Metabolife Int'l Inc.*, 401 F. 3d 1233, 1239 (11th Cir. 2005)). This framing, however, ignores dose/response, which even at the general causation stage, cannot be ignored. The proper inquiry at this stage, as acknowledged even by Plaintiffs' principal authority, is whether the NDMA or NDEA levels to which valsartan patients could reasonably have been exposed increases the risk of the cancers at issue. *See Roundup*, 390 F. Supp. 3d at 1108 ("[At] this general causation phase, the question is whether a reasonable jury could conclude by a preponderance of the evidence that [the substance at issue] can cause [cancer] *at exposure levels people realistically could have experienced*.") (Emphasis added). Plaintiffs' attempt, contrary to their own case law, to exclude dose from the general causation inquiry altogether confirms there is no evidence that exposure at the low levels at issue here causes the cancer(s) alleged.

Similarly, Plaintiffs' reliance on NDMA and NDEA being deemed "probable human carcinogens" by IARC is not relevant to the general causation inquiry. "[The] public health inquiry does not map nicely onto the inquiry required by civil

litigation." *See Roundup*, 390 F. Supp. 3d at 1108. "A substance could be cause for concern, such that it can and should trigger preventive public health measures and further study, even when it is not so clearly dangerous as to allow a verdict in favor of a plaintiff." *Id.* Any statement, whether from a public health agency or from a corporate witness, "conced[ing] that NDMA and NDEA are 'probable human carcinogens'" (Opp. at 30) does not change the necessity of accounting for dose/response to form a reliable general causation opinion.

### D. Dr. Panigrahy's Opinions Regarding Cancer Development in "Downstream Organs" Is Unreliable Because He Does Not State the Level of NDMA Required to Saturate the Liver.

Dr. Panigrahy's opinions regarding the risk of cancer development in "downstream organs" has no scientific support, no matter how many articles Dr. Panigrahy purportedly reviewed, and therefore his opinion is unreliable, *ipse dixit*, and would be misleading to the jury. Plaintiffs fail to address the substance of Defendants' challenge to this opinion anywhere in their Opposition. Dr. Panigrahy does not—and admittedly cannot—identify the level of NDMA that would be necessary to escape metabolism in the liver. The discussion in Dr. Panigrahy's report regarding the bioavailability of NDMA being "dramatically higher" in "larger species" than in rodents, *see* Opp. at 24, is an unspecific generalization that does not address the first pass metabolism capacity of the liver and does not support Dr. Panigrahy's conclusions regarding the alleged risk of cancer development in

downstream organs, let alone cancer development as a result of VCDs. Even if Dr. Panigrahy were able to state the level of NDMA required to saturate the liver, he does not state—and cannot state—whether the level of NDMA *in VCDs* would reach that level or would be excreted by the liver as part of first-pass metabolism on a daily basis.[5] Dr. Panigrahy's opinions with respect to cancer development in downstream organs is unsupported, unreliable and should be excluded for this reason.

## II. DR. PANIGRAHY'S RESEARCH BACKGROUND DOES NOT QUALIFY HIM TO OFFER OPINIONS ON THE CARCINOGENIC EFFECT OF GENOTOXIC COMPOUNDS IN HUMANS.

A witness who meets Rule 702's foundational requirement of being qualified as an expert in one area is not permitted to offer expert testimony in an area unrelated to his general qualifications. *See, e.g.*, *Calhoun v. Yamaha Motor Corp., U.S.A.*, 350 F.3d 316, 322 (3d Cir. 2003) ("An expert may be generally qualified but may lack qualifications to testify outside of his area of expertise."). The expert must be deemed qualified with respect to the *specific opinions* he is offering. *See, e.g.*, *U.S. v. Faines*, 216 Fed. App'x 227, 230 (3d Cir. 2007) (affirming preclusion of fingerprint expert from offering a fingerprint comparison, even though she had

[5] If the level of NDMA and NDEA in VCDs is below the liver's capacity of first-pass metabolism (which Dr. Panigrahy cannot deny since he does not know), not only would downstream organs not be at increased risk, but there would likewise be no accumulation of NDMA, and Dr. Panigrahy's cumulative dose theory likewise fails.

performed an estimated 6,000 fingerprint comparisons in connection with coursework, had extensively read the literature in the field, published one article on the topic of fingerprint analysis, and had taken three courses in fingerprint comparison, because the expert was a research scientist and not a latent fingerprint expert).

Plaintiffs' recitation of Dr. Panigrahy's education and background in cancer research (research relating to cancer treatment) does not address Defendants' specific challenge to Dr. Panigrahy's qualifications. Dr. Panigrahy is not qualified to offer an opinion on the carcinogenic effect of NDMA or NDEA in humas because his research background centers on nongenotoxic mechanisms of extant cancer, not cancer development. Dr. Panigrahy does not study whether specific genotoxic compounds can cause cancer. *See* Panigrahy Dep., Dkt. 1716-4, at 216:23-217:16. He has not studied the effects of NDMA in his academic research, *id*. at 121:6-13, nor has he studied DNA adducts in his academic research. *Id.* at 275:15-18. Dr. Panigrahy only first studied genotoxic compounds once he was retained to serve as an expert in this litigation. *Id.* at 216:23-217:16. The fact that Dr. Panigrahy has his "own" lab (Opp. at 1) does not make him qualified to opine on topics outside his areas of research in that lab. His background and understanding concerning the subject matter of this litigation is, by his own admission, solely the result of time spent reviewing literature with which he has no prior professional experience. That

is not sufficient to qualify him as an expert with respect to the specific opinions on NDMA and NDEA carcinogenicity in humans that he seeks to offer in this case.

Plaintiffs' arguments and cases for the proposition that a medical doctor need not be an epidemiologist to testify regarding epidemiological studies do not address the substance of Defendants challenge to Dr. Panigrahy's qualifications. Moreover, those cases all involved clinicians. *See generally Danley v. Bayer (In re Mirena IUD Prods. Liab. Litig.)*, 169 F. Supp. 3d 396, 426 (S.D.N.Y. 2016); *Roundup*, 390 F. Supp. 3d at 1148. Dr. Panigrahy has never been a clinician and is not licensed to practice medicine in any jurisdiction. Panigrahy Dep., Dkt. 1716-4, at 80:13-16. A clinician offering opinions based on studies he or she routinely reviews in treating patients is not analogous to a researcher offering opinions outside of his area of research, simply because he holds an M.D. degree. Defendants respectfully submit that the Court should determine that Dr. Panigrahy does not meet the minimum qualifications based on his knowledge, skill, experience, training, or education to be able to offer an opinion as to whether the NDMA or NDEA in VCDs causes cancer and should exclude his testimony.

## CONCLUSION

Based on the above-cited authority, and the authority cited in Defendants' initial Memorandum of Law, Defendants respectfully request that the Court exclude Dr. Panigrahy's opinions. Dr. Panigrahy is not qualified to offer the opinions he

offers. Moreover, he uses a flawed methodology, which renders his opinions unhelpful, unreliable, and inadmissible under Rule 702 and *Daubert*. For these reasons as set forth above, the Court should exclude or, in the alternative, limit Dr. Panigrahy's opinions.

Dated: January 6, 2022

By: */s/ Seth A. Goldberg*
Seth A. Goldberg, Esq.
*Liaison Counsel for Defendants*

DUANE MORRIS LLP
Seth A. Goldberg, *Liaison Counsel for Defendants*
Jessica Priselac, *Liaison Counsel for Defendants*
30 South 17th Street
Philadelphia, Pennsylvania 19103
Tel.: (215) 979-1000
Fax: (215) 979-1020
SAGoldberg@duanemorris.com
JPriselac@duanemorris.com

*Counsel for Zhejiang Huahai Pharmaceutical Co, Ltd., Huahai U.S., Inc., Prinston Pharmaceutical Inc., and Solco Healthcare US, LLC*

GREENBERG TRAURIG, LLP
Lori G. Cohen
Victoria Davis Lockard
Steven M. Harkins
Terminus 200
3333 Piedmont Road, N.E.,
Suite 2500
Atlanta, Georgia 30305
(678) 553-2100
(678) 553-2386 (facsimile)
CohenL@gtlaw.com
LockardV@gtlaw.com
HarkinsS@gtlaw.com

*Counsel for Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd., Actavis Pharma, Inc., and Actavis LLC*

PIETRAGALLO GORDON ALFANO BOSICK & RASPANTI, LLP
Clem C. Trischler
Jason M. Reefer
Frank H. Stoy
38th Floor, One Oxford Centre
Pittsburgh, Pennsylvania 15219
Tel: (412) 263-2000
Fax: (412) 263-2001
CCT@PIETRAGALLO.com

*Counsel for Mylan Laboratories, Ltd. and Mylan Pharmaceuticals, Inc.*

BARNES & THORNBURG LLP
Sarah E. Johnston, *Liaison Counsel for Retailer Defendants*
Kara Kapke
Kristen L. Richer
2029 Century Park East, Suite 300
Los Angeles, CA 90067
Tel: (310) 284-3798
Fax: (310) 284-3894
Sarah.Johnston@btlaw.com
Kara.Kapke@btlaw.com
Kristen.Richer@btlaw.com

*Counsel for CVS Pharmacy, Inc. (incorrectly named as CVS Health Corporation)*

ULMER & BERNE LLP
Jeffrey D. Geoppinger, *Liaison Counsel for Wholesaler Defendants*
600 Vine Street, Suite 2800
Cincinnati, OH 45202-2409
Tel.: (513) 698-5038
Fax: (513) 698-5039

jgeoppinger@ulmer.com

*Counsel for AmerisourceBergen Corporation*

**CERTIFICATE OF SERVICE**

I HEREBY CERTIFY that on January 6, 2022, I electronically filed the foregoing with the Clerk of the Court by using the CM/ECF system which will send a notice of electronic filing to all CM/ECF participants in this matter.

*/s/ Seth A. Goldberg*
Seth A. Goldberg

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